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## ISOBUTYLGABA AND ITS DERIVATIVES FOR THE TREATMENT OF PAIN

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

Notice: more than one reissue application has been filed for the reissue of U.S. Pat. No. 6,001,876. The reissue applications: are U.S. application Ser. No. 12/700,968 (filed Feb. 105, 2010), which is a continuation of the present application; and, the present application.

This application claims benefit of Provisional application Ser. No. 60/022,337, Jul. 24, 1996.

## BACKGROUND OF THE INVENTION

The present invention is the use of analogs of glutamic acid and gamma-aminobutyric acid (GABA) in pain therapy, as the compounds exhibit analgesic/antihyperalgesic action. Advantages of the use of the compounds includes the finding that repeated use does not lead to tolerance nor is there a cross-tolerance between morphine and the compounds.

The compounds of the invention are known agents useful in antiseizure therapy for central nervous system disorders such as epilepsy, Huntington's chorea, cerebral ischemia, Parkinson's disease, tardive dyskinesia, and spasticity. It has also been suggested that the compounds can be used as antidepressants, anxiolytics, and antipsychotics. See WO 92/09560 (U.S. Ser. No. 618,692 filed Nov. 27, 1990) and WP 93/23383 (U.S. Ser. No. 886,080 filed May 20, 1992).

## SUMMARY OF THE INVENTION

The instant invention is a method of using a compound of Formula I below in the treatment of pain, especially for treatment of chronic pain disorders. Such disorders include, but are not limited to, inflammatory pain, postoperative pain, osteoarthritis pain associated with metastatic cancer, trigeminal neuralgia, acute herpetic and postherpetic neuralgia, diabetic neuropathy, causalgia, brachial plexus 40 avulsion, occipital neuralgia, reflex sympathetic dystrophy, fibromyalgia, gout, phantom limb pain, [bum] burn pain, and other forms of neuralgic, neuropathic, and idiopathic pain syndromes.

A compound are those of Formula I

or a pharmaceutically acceptable salt thereof wherein

 $R_1$  is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;

R<sub>2</sub> is hydrogen or methyl; and

R<sub>3</sub> is hydrogen, methyl, or carboxyl.

Diastereomers and enantiomers of compounds of Formula 60 I are included in the invention.

Preferred compounds of the invention are those according to claim 1 wherein  $R_3$  and  $R_2$  are hydrogen, and  $R_1$  is  $-(CH_2)_{0-2}$ —i  $C_4H_9$  as an (R), (S), or (R,S) isomer.

The more preferred compounds of the invention are (S)-3-65 (aminomethyl)-5-methylhexanoic acid and 3-aminomethyl-5-methyl-hexanoic acid.

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## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1. Effect of Gabapentin (1-(aminomethyl)-cyclohexaneacetic acid), CI-1008 ((S)-3-(aminomethyl)-5-methylhexanoic acid), and 3-aminomethyl-5-methylhexanoic acid in the Rat Paw Formalin Test

Test compounds were administered s.c. 1 hour before an intraplantar injection of 50  $\mu$ L formalin. The time spent licking/biting the injected paw during the early and late phases was scored. Results are shown as the mean  $\pm$ SEM of 6 to 8 animals per group. \*P<0.05 and \*\*P<0.01 significantly different from vehicle (Veh.) treated controls (ANOVA followed by Dunnett's t-test).

FIG. 2. Effect of Gabapentin and CI-1008 on 15 Carrageenin-Induced Mechanical Hyperalgesia

Nociceptive pressure thresholds were measured in the rat using the paw pressure test. Baseline (BL) measurements were taken before animals were administered with 100  $\mu L$  of 2% carrageenin by intraplantar injection. Results are shown as mean (±SEM) of 8 animals per group. Gabapentin (GP), CI-1008, or morphine (MOR; 3 mg/g) was administered s.c. 3.5 hours after carrageenin. \*P<0.05 and \*\*P<0.01 significantly different from vehicle control group at the same time point (ANOVA followed by Dunnett's t-test).

FIG. 3. Effect of Gabapentin and CI-1008 on Carrageenin-Induced Thermal Hyperalgesia

Nociceptive thermal thresholds were measured in the rat using the Hargreaves apparatus. Baseline (BL) measurements were taken before animal s were administered with  $100~\mu L$  of 2% carrageenin by intraplantar injection. Results are shown as mean ( $\pm {\rm SEM})$  of 8 animals per group. Gabapentin (GP) or CI-1008 was administered s.c. 2.5 hours after carrageenin. \*P<0.05 and \*\*P<0.01 significantly different from vehicle control group at the same time point (ANOVA followed by Dunnett's t-test).

FIG. **4**. Effect of (a) Morphine, (b) Gabapentin, and (c) S-(+)-3-Isobutylgaba on Thermal Hyperalgesia in the Rat Postoperative Pain Model

Gabapentin or S-(+)-3 isobutylgaba was administered 1 hour before surgery. Morphine was administered 0.5 hour before surgery. Thermal paw withdrawal latencies (PWL) were determined for both ipsilateral and contralateral paws using the rat plantar test. For clarity contralateral paw data 45 for drug-treated animals is not shown. Baseline (BL) measurements were taken before surgery and PWL were reassessed 2, 24, 48, and 72 hours postsurgery. Results are expressed as the mean PWL(s) of 8 to 10 animals per group (vertical bars represent ±SEM). \*P<0.05 \*\*P<0.01 significantly different (ANOVA followed by Dunnett's t-test), comparing ipsilateral paw of drug-treated groups to ispsilateral paw of vehicle-treated group at each time point. In the figure, — is vehicle contralateral, — is vehicle ispsilateral,  $-\Delta$ — is 1 mg/kg morphine,  $-\Box$ — is 3, and  $-\lozenge$  — is 6 for morphine in 4a. In 4b, — $\Delta$ — is 3, — $\Box$  is 10, and  $-\diamondsuit$ — is 30 for gabapentin. In 4c,  $-\Delta$ — is 3 mg/kg,  $-\Box$  is 10, and  $-\Diamond$  is 30 for S-(+)isobutylgaba.

FIG. **5** Effect of (a) Morphine, (b) Gabapentin, and (c) S-(+)-3-Isobutylgaba on Tactile Allodynia in the Rat Postoperative Pain Model

Gabapentin or S-(+)-3-isobutylgaba was administered 1 hour before surgery. Morphine was administered 0.5 hour before surgery. Paw withdrawal thresholds to von Frey hair filaments were determined for both ipsilateral and contralateral paws. For clarity, contralateral paw data for drug-treated animals is not shown. Baseline (BL) measurements were